

APPROVED	O G. FIG.
BY	CLASS
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le: Production of Human Parathyroid Hormone
 From Microorganisms
 Inventor(s): Kaare M. GAUTVIK, et al.
 Appl. No.: 09/287,332
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FIG. 1

DNA SEQUENCE FOR HUMAN PREPROPARATHYROID HORMONE

```

      10              30              50
ATGATHCCNGCNAARGAYATGGCNAARGTNATGATHGTNATGYTNGCNATHTGYTTYTIN

      70              90              110
ACNAARWSNGAYGGNAARWSNGTNAARAARMGNWSNGTNWSNGARATHCARYTNATGCAY

      130             150             170
AAYYTNGGNAARCAYYTNAAYWSNATGGARMGNGTNGARTGGYTNGMNAARAARYTNCAR

      190             210             230
GAYGTNCAYAAAYTTYGTNGCNYTNGGNGCNCNYTNGCNCNMGNAYGCNGGNNWNCAR

      250             270             290
MGNCNMGNAAARAARGARGAYAAYGTNYTNGTNGARWSNCAYGARAARWSNYTNGGNGAR

      310             330
GCNGAYAARGCNGAYGTNAAYGTNYTNACNAARGCNAARWSNCARTTR
  
```

H = A OR C
 R = A OR G
 W = A OR T
 S = C OR G
 Y = C OR T
 H = A OR C OR T
 N = A OR G OR C OR T

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FIG. 2

DNA SEQUENCE FOR HUMAN
PREPROPARATHYROID HORMONE IN PLASMID pSSHPTH-10

```

      10              30              50
TATGATGATACCTGCAAAAGACATGGCTAAAGTTATGATTGTCATGTTGGCAATTTGTTT

      70              90              110
TCTTACAAAATCGGATGGGAAATCTGTTAAGAAGAGATCGTGGAGTGAATACAGCTTAT

      130             150             170
GCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGCGTAAGAAGCT

      190             210             230
GCAGGATGTGACAATTTTGTGCGCTTGGAGCTCCTCTAGCTCCAGAGATGCTGTTT

      250             270             290
CCAGAGGCCCCGAAAAAGGAAGACAATGTCTTGTTGAGAGCCATGAAAAAGTCTTGA

      310             330
GAGGCAGACAAAGCTGATGTGAATGTATTAAGCTAAAGCTAAATCCCAAGTGA

```

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FIG. 3

PORTION OF DNA SEQUENCE OF THE PLASMID
 FOR INSERTION INTO E. COLI, CODING FOR HUMAN
 PREPROPARATHYROID HORMONE WITH FLANKING SEQUENCES.

10 30 50
 TATGATGATHCCNGCNAARGAYATGGCNAARGTNATGATHGTNATGYTNGCNATHGTGTT
 70 90 110
 YYTNACNAARNSNGAYGGNAARNSNGTNAARAARHNSNGTNSNGARATHCARYTNAT
 130 150 170
 GCAYAAYTTNGGNAARCAYYTNAAYWSNATGGARMGNGTNGARTGGYTNGNAARAARYT
 190 210 230
 NCARGAYGTNCAYAAYTTYGTNGCNYTNGGNGCNCNYTNGCNCNMGNAGAYGCNGGNWS
 250 270 290
 NCARMGNCNMGNARAARGARGAYAAYGTNYTNGTNGARWSNCAYGARAARWSNYTNGG
 310 330 350
 NGARGCNGAYAARGCNGAYGTNAAYGTNYTNACNAARGCNAARWSNCARTPRAAATGAAA
 370 390 410
 ACAGATATTGTCAGAGTTCTGCTCTAGACAAGTGTAGGGCAACAATACATGCTGCTAATTC
 430
 AAAGCTCTATTA

M = A OR C
 R = A OR G
 W = A OR T
 S = C OR T
 Y = C OR T
 H = A OR C OR T
 N = A OR G OR C OR T

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FIG. 4

DNA SEQUENCE FOR HUMAN PREPROPARATHYROID
HORMONE IN PLASMID pSSHPTH-10 WITH FLANKING SEQUENCES

```

      10              30              50
TATGATGATACCTGCAAAAGACATG6CTAAAGTTATGATTGTCATGTTG6CAATTGTTT

      70              90              110
TCTTACAAAATCGGATGGGAAATCTGTTAAGAAGAGATCTGTGAGTGAATACAGCTTAT

      130             150             170
GCATAACCTG6GAAAACATCTGAACTCGATGGAGAGAGTAGAATG6CTGCGTAAGAAGCT

      190             210             230
GCAGGATGTGCACAATTTTGTG6CCCTTG6AGCTCCTCTAGCTCCAGAGATGCTG6TTC

      250             270             290
CCAGAGGCCCCGAAAAAAGGAAGACAATGTCTTGGTTGAGAGCCATGAAAAAGTCTTGG

      310             330             350
AGAGGCAGACAAAGCTGATGTGAATGTATTAAGTAAAGCTAAATCCAGTGAAAAATGAAA

      370             390             410
ACAGATATTGTCAGAGTTCTGCTCTAGACAGTGTAG6GCAACAATACATGCTGCTAATTC

      430
AAAGCTCTATTA

```

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FIG. 5

DNA SEQUENCE CODING FOR PREPROPARATHYROID HORMONE
 IN pSSHPTH-10 WITH FLANKING SEQUENCES, SHOWING
 THE CORRESPONDING AMINO ACID SEQUENCE OF
 PREPROPARATHYROID HORMONE

10	30	50
TATGATGATACCTGCAAAAGACATGGCTAAAGTTATGATTGTCATGTTGGCAATTTGTTT		
MetIleProAlaLysAspMetAlaLysValMetIleValMetLeuAlaIleCysPh		
70	90	110
TCTTACAAAATCGGATGGGAAATCTGTTAAGAAGAGATCTGTGAGTGAATACAGCTTAT		
eLeuThrLysSerAspGlyLysSerValLysLysArgSerValSerGluIleGlnLeuMe		
130	150	170
GCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGCGTAAGAAGCT		
tHisAsnLeuGlyLysHisLeuAsnSerMetGluArgValGluTrpLeuArgLysLysLe		
190	210	230
GCAGGATGTGCACAATTTTGTGGCCCTTGGAGCTCCTCTAGCTCCAGAGATGCTGGTTC		
uGlnAspValHisAsnPheValAlaLeuGlyAlaProLeuAlaProArgAspAlaGlySe		
250	270	290
CCAGAGGCCCGAAAAAGGAAGACAATGTCTTGGTTGAGAGCCATGAAAAAGTCTTGG		
rGlnArgProArgLysLysGluAspAsnValLeuValGluSerHisGluLysSerLeuG1		
310	330	350
AGAGGCAGACAAAAGCTGATGTGAATGTATTAAGTAAAGCTAAATCCAGTGAAAAATGAAA		
yGluAlaAspLysAlaAspValAsnValLeuThrLysAlaLysSerGlnEnd		
370	390	410
ACAGATATTGCAGAGTTCTGCTCTAGACAGTGTAGGGCAACAATACATGCTGCTAATTC		
430		
AAAGCTCTATTA		

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FIG. 6

NUCLEOTIDE SEQUENCE OF THE MF 1-HPTH FISION-GENE FROM pS LX5-HPTH1.
NUCLEOTIDE NOS. 1-173 MAKEUP THE MH 1 PROMOTER REGION AND 5'
NONCODING SEQUENCE. 174-440 IS THE MF 1 N-TERMINAL CODING
SEQUENCE. 441-695 IS THE HPTH SEQUENCE OBTAINED FROM pSSHPTH-10.
696-726 IS AN HPTH 3' NONCODING SEQUENCE FROM pSSHPTH-10. 727-732
IS FROM pUC19. 733-874 IS MF 1 3' NONCODING SEQUENCE AND
TRANSCRIPTIONAL TERMINATION SIGNAL.

```

      10              30              50
AGTGAAGAAAACAAAAAGCAACAACAGGTTTTGGATAAGTACATATATAAGAGGGCCT
      70              90              110
TTTGTTC CATCAAAAATGTTACTGTTCTTACGATTCATTTACGATTCAAGAATAGTTCA
      130             150             170
AACAGAAGATTACAACTATCAATTTATACACAATATAAACGACCAAAAGAATGAGAT
      190             210             230
TTCCTTCAATTTTTACTGCAGTTTTATTGCGAGCATCCTCCGCATTAGCTGCTCCAGTCA
      250             270             290
ACACTACAACAGAAGATGAAACGGCACAAATTCCGGCTGAAGCTGTCATCGGTTACTCAG
      310             330             350
ATTTAGAAGGGGATTTGATGTTGCTGTTTTGCCATTTTCCAACAGCACAAATAACGGGT
      370             390             410
TATTGTTTATAAATACTACTATTGCCAGCATTGCTGCTAAAGAAGAAGGGGTATCTTTGG
      430             450             470
ATAAAAGAGAGGCTGAAGCTTCTGTGAGTGAAATACAGCTTATGCATAACCTGGGAAAAC
      490             510             530
ATCTGAACCTCGATGGAGAGAGTAGAATGGCTGCGTAAGAAGCTGCAGGATGTGCACAATT
      550             570             590
TTGTTGCCCTTGGAGCTCCTCTAGCTCCCAGAGATGCTGGTTCCCAGAGGCCCGAAAAA
      610             630             650
AGGAAGACAATGTCTTGTTGAGAGCCATGAAAAAGTCTTGGAGAGGCAGACAAAGCTG
      670             690             710
ATGTGAATGTATTAATAAGCTAAATCCAGTGAAAATGAAAACAGATATTGTCAGAGT
      730             750             770
TCTGCTCTAGAGTCGACTTTGTTCCCACTGTACTTTTAGCTCGTACAAAATACAATATAC
      790             810             830
TTTTCAATTTCTCCGTAAACAACCTGTTTTCCCATGTAATATCCTTTTCTATTTTTCGTTT
      850             870
CGTTACCAACTTTACACATACTTTATATAGCTAT

```

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FIG. 7

PARTIAL DNA SEQUENCE FOR THE PLASMID FOR INSERTION INTO YEAST
IN WHICH: NUCLEOTIDE NOS. 1-173 MAKEUP THE MF 1 PROMOTER
REGION AND 5' NONCODING SEQUENCE. 174-440 IS THE MF 1 N-TERMINAL
CODING SEQUENCE. 441-695 IS AN HPTH SEQUENCE. 696-726 IS AN
HPTH 3' NONCODING SEQUENCE FROM pSSHPTH-10. 727-732 IF FROM
PUC19. 733-874 IS MF 1 3' NONCODING SEQUENCE AND TRANSCRIPTIONAL
TERMINATION SIGNAL.

```

10          30
AGTGAAGAAAACCAAAAAGCAACAACAGGTTTTGGATAAGTACATATATAAGAGGGCCT
70          90          110
TTTGTTCATCAAAAATGTTACTGTTCTTACGATTCATTTACGATTCAAGAATAGTTCA
130         150         170
AACAGAAGATTACAACTATCAATTTATACACAATATAAACGACCAAAAGAATGAGAT
190         210         230
TTCCTTCAATTTTTACTGCAGTTTTATTTCGCAGCATCCTCCGATTAGCTGCTCCAGTCA
250         270         290
ACACTACAACAGAAGATGAAACGGCACAAATTCGGCTGAAGCTGTCATCGGTTACTCAG
310         330         350
ATTTAGAAGGGGATTTTCGATGTTGCTGTTTTGCCATTTCCAACAGCACAAATAACGGGT
370         390         410
TATTGTTTATAAATACTACTATTGCCAGCATTGCTGCTAAAGAAGAAGGGGTATCTTTGG
430         450         470
ATAAAGAGAGGCTGAAGCTWSNGTWSNGARATHCARYTNATGCAYAAYYTNGGNAARC
490         510         530
AAYTNAAYWSNATGGARMNGTNGARTGGYTNGMNAARAARYTNCARGAYGTNCAYAAYT
550         570         590
TYGTNGCNYTNGGNGCNCNYTNGCNCNMNGAYGCNGGWSNCARMGNCNMGNAARA
610         630         650
ARGARGAYAAYGTNYTNGTNGARWSNCAYGARAARWSNYTNGGNGARGCNGAYAARGCNG
670         690         710
AYGTNAAYGTNYTNACNAARWSNCARTTAAATGAAAACAGATATTGTCAGAGT
730         750         770
TCTGCTCTAGAGTCGACTTTGTTCCCACTGTACTTTTAGCTCGTACAAAATACAATATAC
790         810         830
TTTTCATTTCTCCGTAAACAACCTGTTTTCCCATGTAATATCCTTTTCTATTTTTCGTTT
850         870
CGTTACCAACTTTACACATACTTTATATAGCTAT, WHEREIN

```

M = A OR C
R = A OR G
W = A OR T
S = C OR G
Y = C OR T
H = A OR C OR T
N = A OR G OR C OR T

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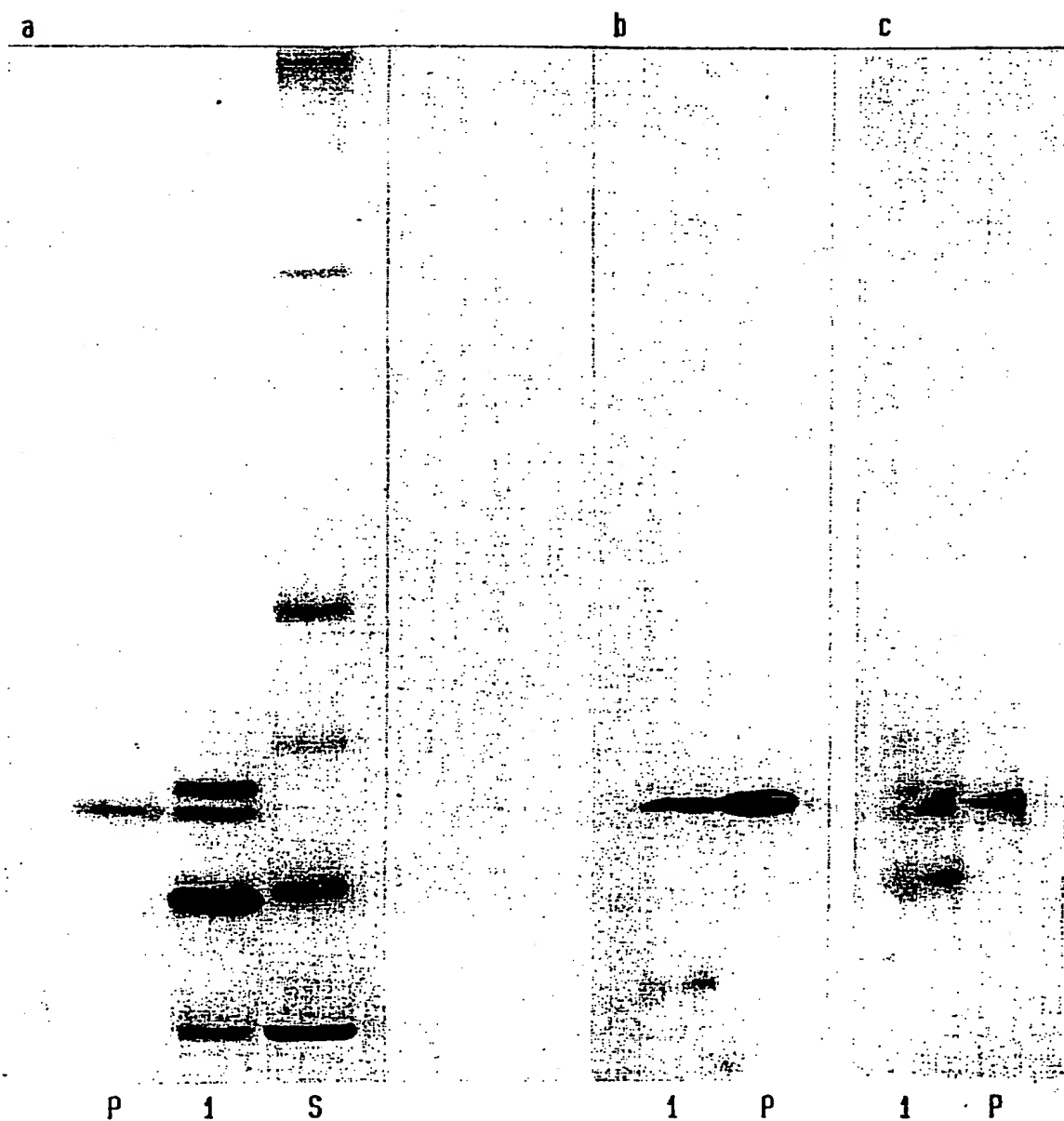
Production of Human Parathyroid Hormone
From Microorganisms

Inventor(s): Kaare M. GAUTVIK, et al.

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FIG. 8

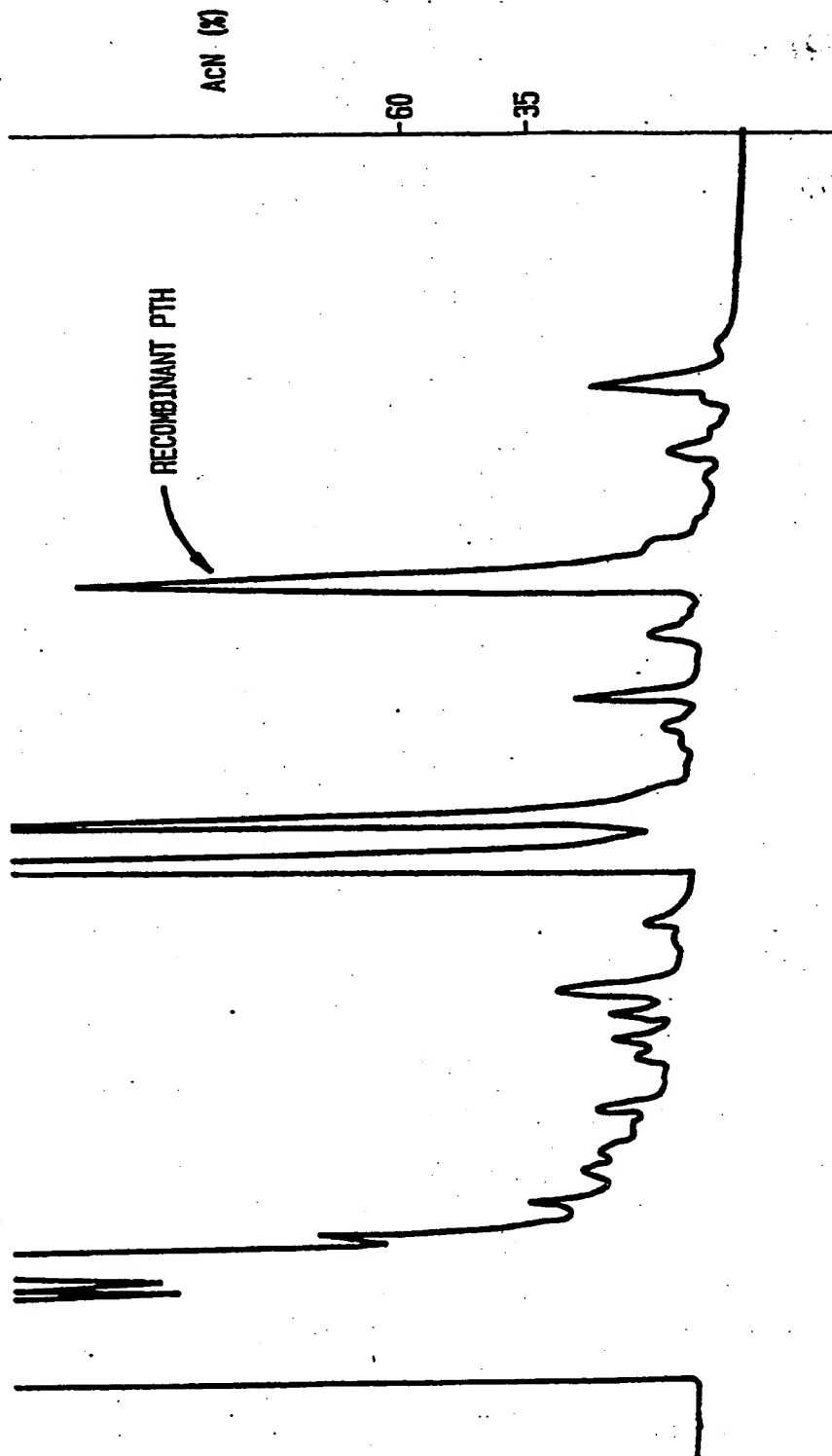


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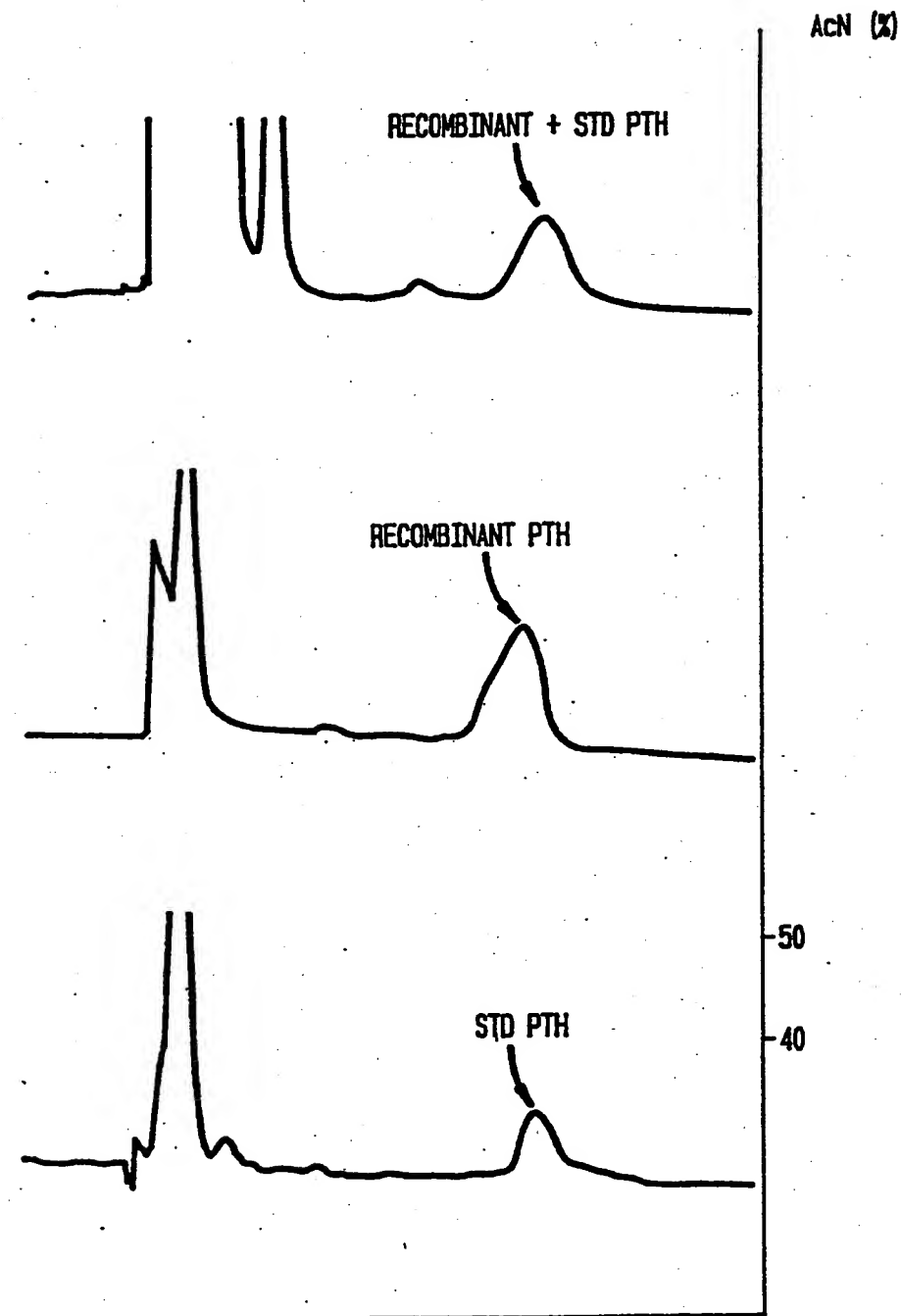
FIG. 9A



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FIG. 9B



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FIG. 10A

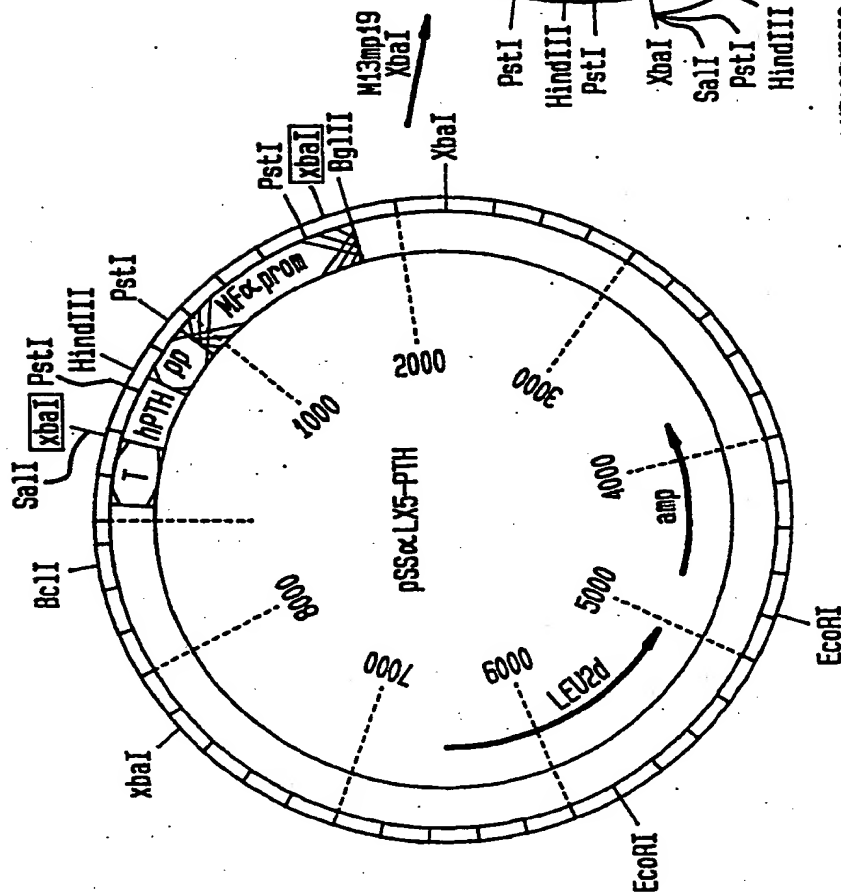
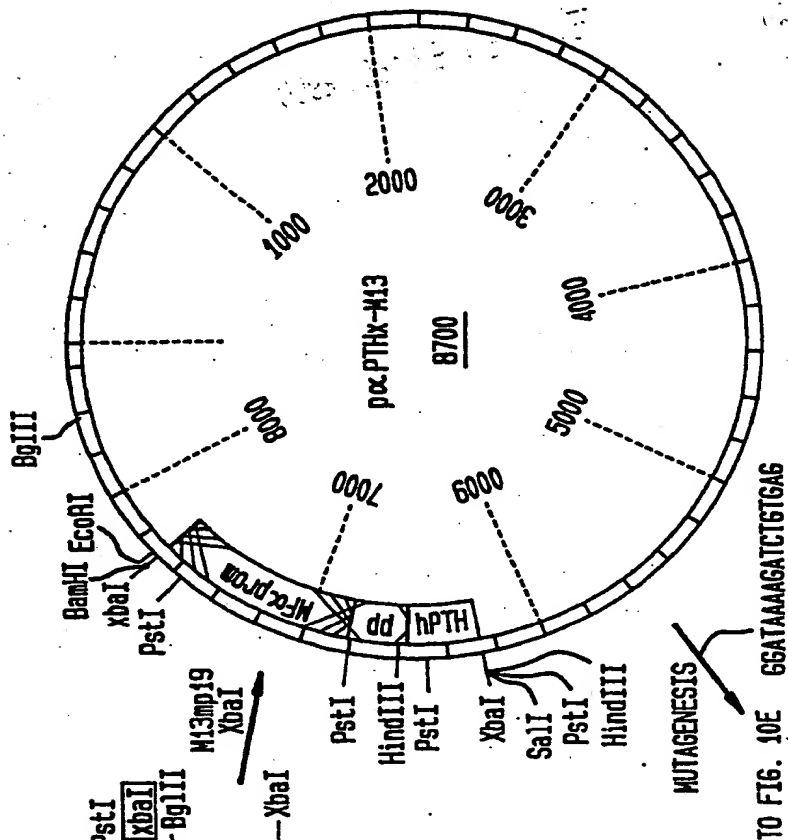


FIG. 10B



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FIG. 10F

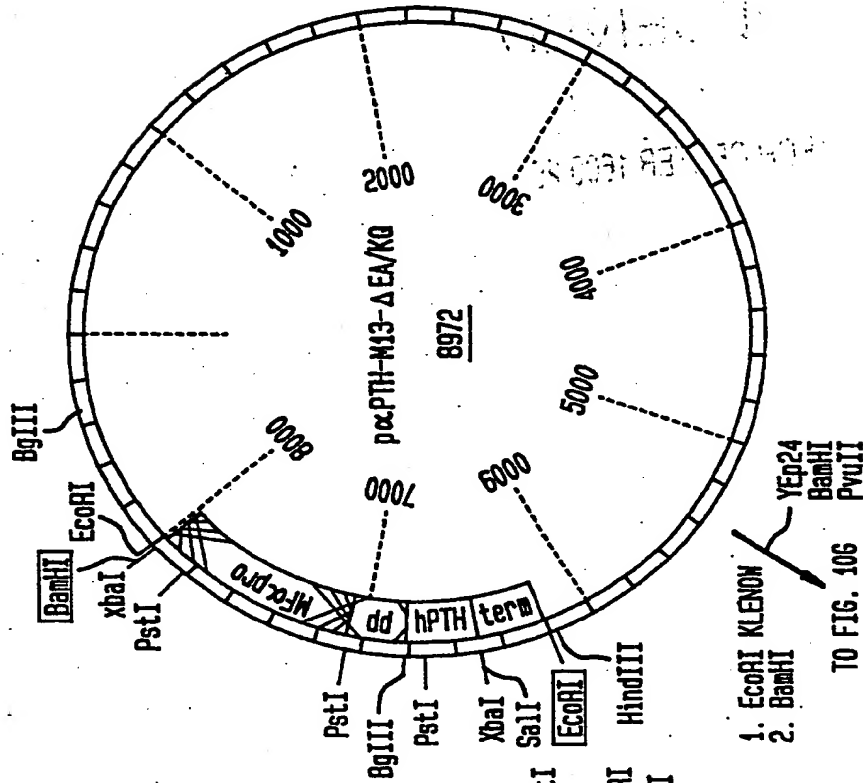
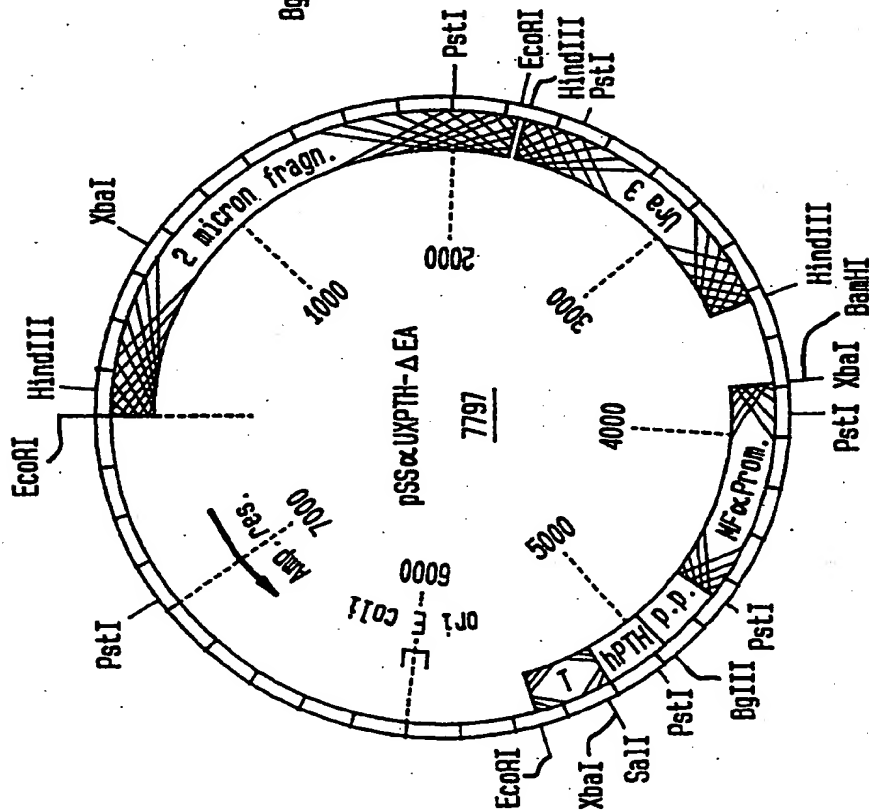


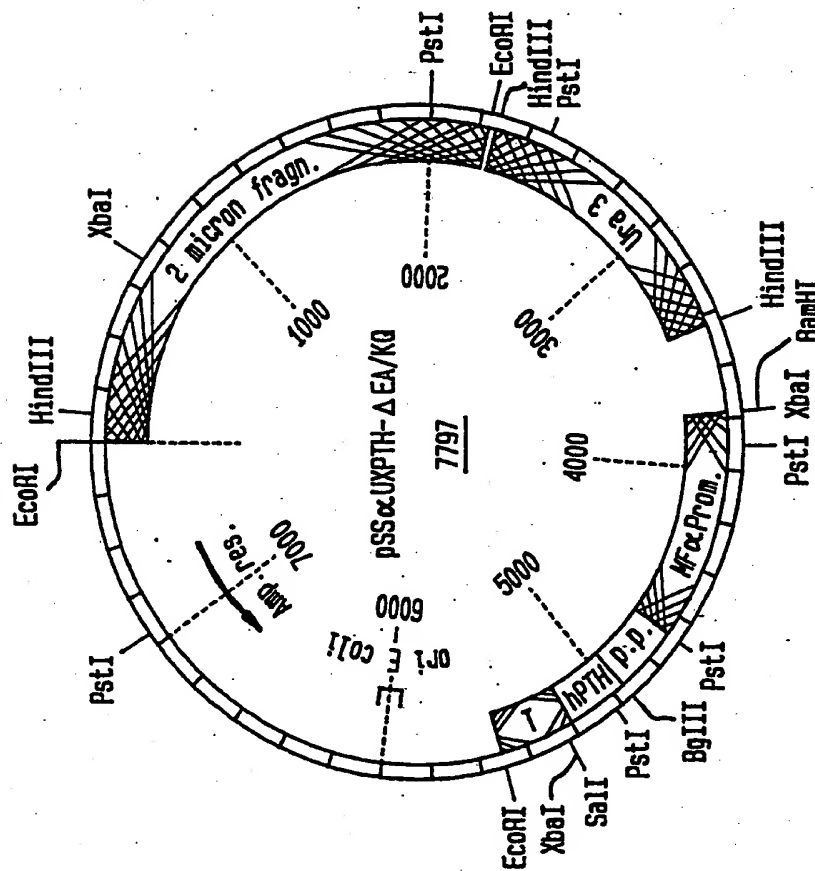
FIG. 10E



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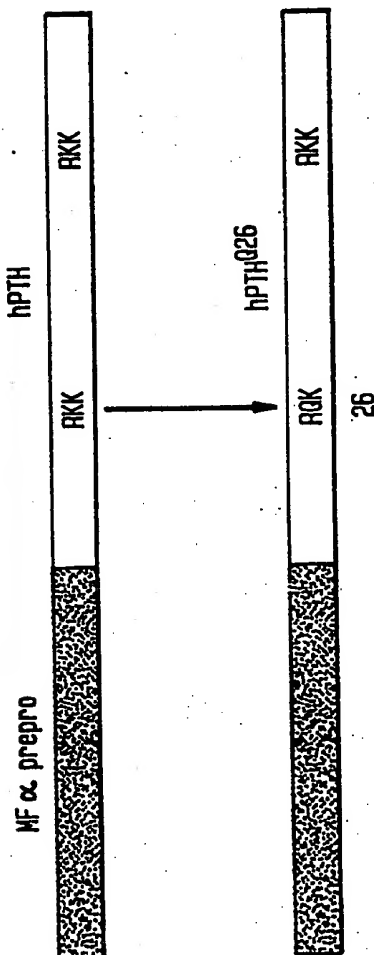
FIG. 10G



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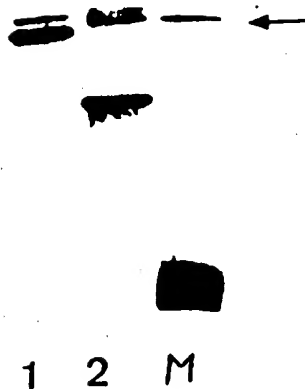
FIG. 11
IN vitro MUTAGENESIS OF hPTH



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FIG. 12



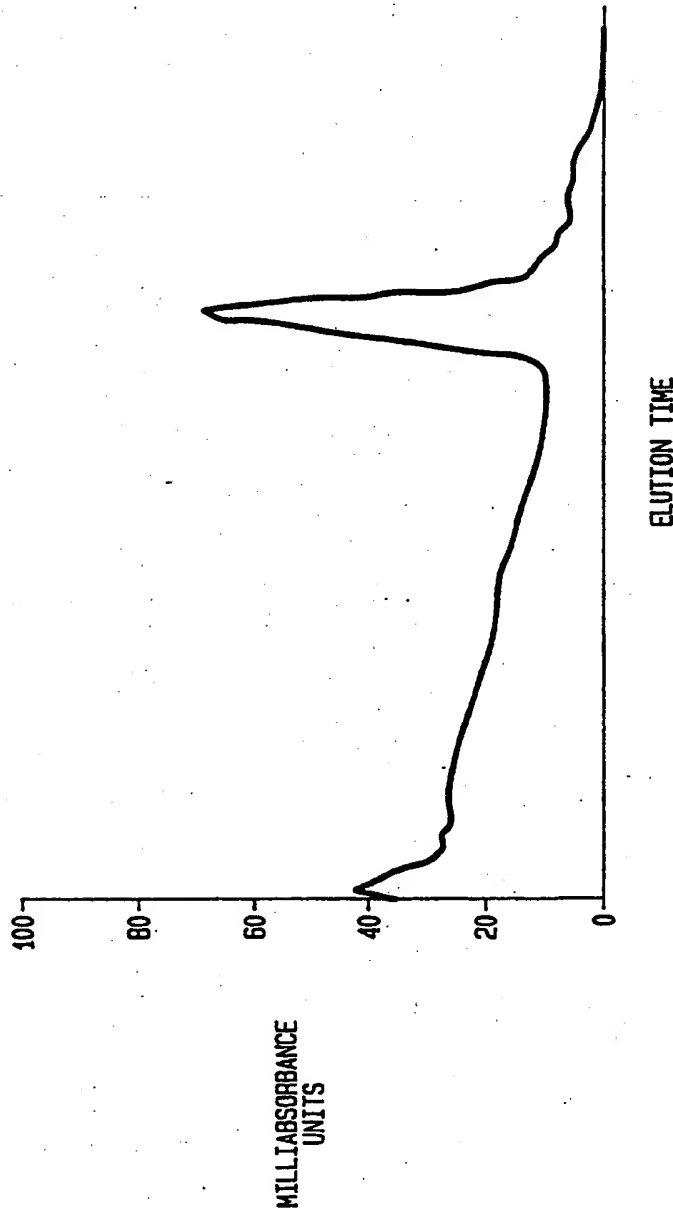
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FIG. 13A

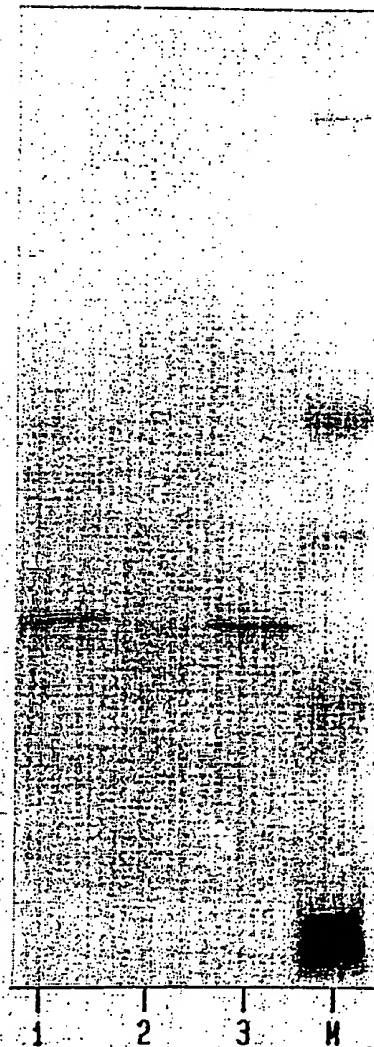
HPLC CHROMATOGRAM OF hPTH (Q26)



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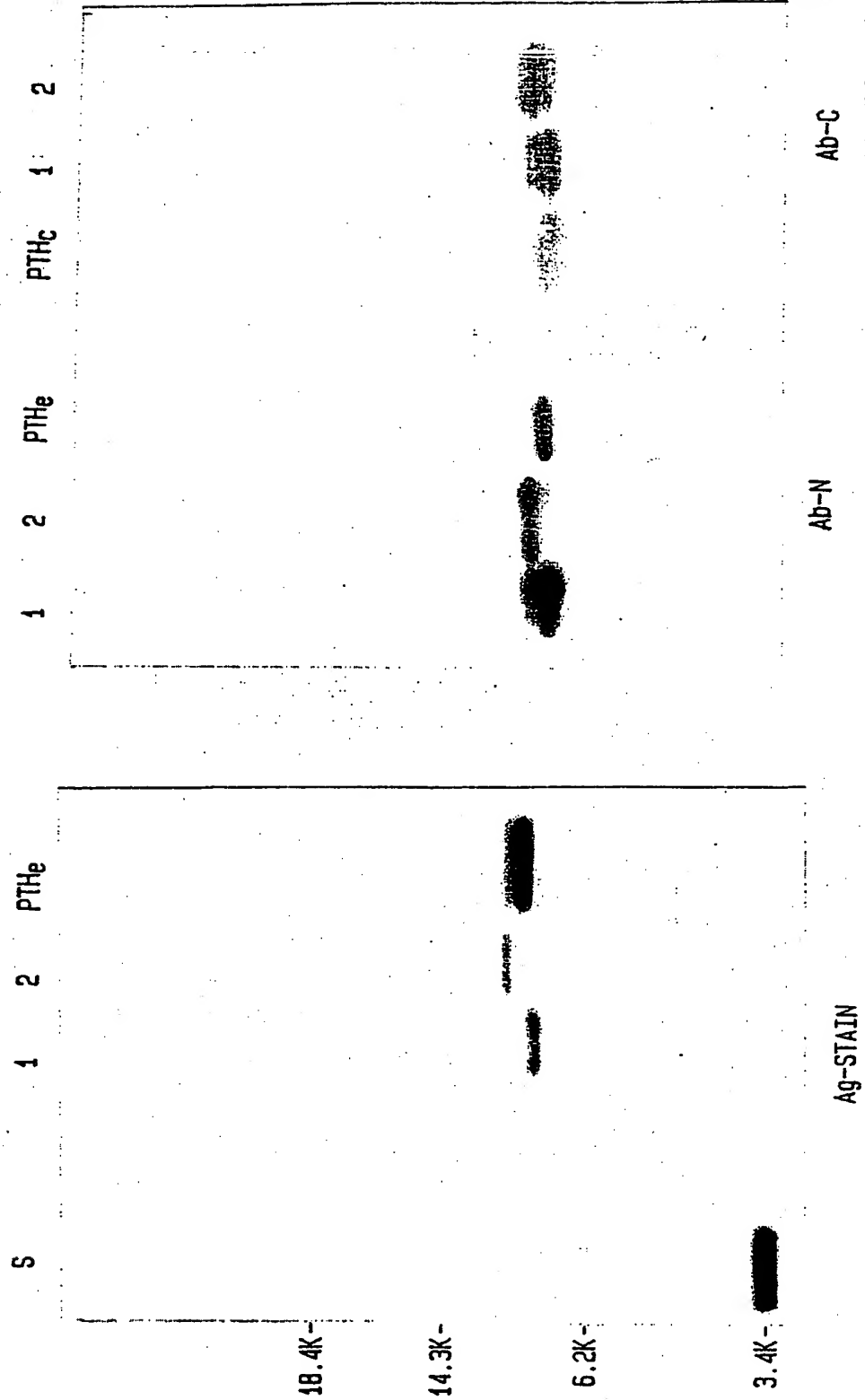
FIG. 13B



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FIG. 14



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FIG. 15

